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Editorial Review

Novel anti-inflammatory drugs in hypertension

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'Atherosclerosis is a chronic inflammatory disease induced by cholesterol . . .'

Rudolf Virchow (1821–1902)

As suggested by Virchow more than a century ago, inflammation plays a pivotal role in atherogenesis and potentially also in the pathogenesis of hypertension and its sequelae. As such, the current review focuses on the role of inflammation in hypertension and emerging therapeutical approaches.

Inflammation and cardiovascular risk

Clinical data

Over the last years chronic low-grade inflammation has emerged as an important new cardiovascular risk factor. Inflammatory responses within the vasculature might release pro-inflammatory cytokines that increase levels of C-reactive protein (CRP). First evidence for a role of inflammation in the development of atherosclerosis comes from studies demonstrating its prognostic value in unstable angina [1]. The inflammation hypothesis was further supported by data from observational studies demonstrating that CRP is a predictor of first cardiovascular events and might be an even stronger prognostic factor than low-density lipoprotein (LDL)-Cholesterol for coronary artery disease [2,3]. CRP appears to be a stable analyte over time and has been subject to numerous recent studies. Thus, on the basis of several studies, the Centers for Disease Control and Prevention and the American Heart Association recommended using highly sensitive (hs)-CRP and implicated the relative risk categories (low, average, high), corresponding to approximate tertiles of values (<1.0, 1.0 to 3.0 and >3.0 mg/l, respectively) for individual cardiovascular risk assessment, in particular for those patients presenting with an intermediate risk [4]. However, a single inflammatory marker may or may not estimate all aspects of the underlying inflammatory processes, especially as they may affect cardiovascular disease (CVD) risk, and different markers may differ in their specificity for CVD. Indeed, there are several additional markers with a potential role as useful predictors of cardiovascular risk, such as serum amyloid-A, cytokines (e.g. interleukin (IL)-6), acute phase reactants, adhesion molecules and fibrinogen.

Interestingly, a recent publication demonstrated that significant gender and race differences in CRP levels exist which contribute to differences in cardiovascular outcome [5]. CRP plasma levels were assessed in 2749 white and black subjects aged 30–65 years and participating in the Dallas Heart Study. Black subjects had higher CRP levels than white subjects and women had higher CRP levels than men, suggesting that overall recommendations for CRP cut-off levels for risk assessment should be adjusted for race and gender. The clinical relevance of CRP as a significant predictor of coronary artery disease (CAD) was further challenged by Danesh *et al.* [6], demonstrating that CRP was a weaker marker than traditional risk factors like total cholesterol or smoking in the Reykjavik prospective study. However, in the study population, total plasma cholesterol levels were higher and CRP levels lower than those reported in the US population.

Experimental data

Experimental data demonstrate that CRP may exert effects on the vasculature. Indeed, CRP induces ICAM-1, VCAM-1 and MCP-1 expression in endothelial cells [7,8], upregulates angiotensin II type 1 receptors in human vascular smooth muscle cells [9] and CRP opsonization of low-density lipoprotein (LDL) mediates LDL uptake by macrophages [10]. CRP inhibits the expression of NO synthase via translational and post-translational mechanisms, resulting in reduced

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NO bioavailability, and stimulates the release of ET-1, IL-6 and vasoconstrictive peptides in human endothelial cells [11,12]. Interestingly, CRP levels correlate to endothelial dysfunction in patients with angiographically normal coronary arteries, established CAD and acute coronary syndromes [13–15]. A recent publication demonstrated specific receptors for CRP on human aortic endothelial cells [17]. After binding to FC gamma receptors I and II, CD64 and CD32 respectively, CRP reduces eNOS activity and prostacyclin levels and increases interleukin-8, ICAM-1 and VCAM-1. These pro-inflammatory effects were prevented with specific antibodies to CD32 and CD64. However, CRP elicits potential vasoprotective effects such as endothelium-independent vasorelaxing effects in human vessels *in vitro* [16].

In addition, opposing effects of native and modified CRP have been reported. Indeed, native CRP promotes while modified CRP attenuates the development of atherosclerotic lesions in ApoE knockout mice [18]. Verma *et al*. [12] showed that CRP inhibited both basal and vascular endothelial growth factor (VEGF)-stimulated angiogenesis, which would in turn inhibit plaque neovascularization. Furthermore, recent publications suggest, that CRP independent mechanisms like azide and lipopolysaccharide, but not CRP itself, might cause some of the observed effects on endothelial cells [76,77].

Inflammation and endothelial function

Endothelial function has evolved as a surrogate for the development and progression of atherosclerotic disease. Indeed, impaired endothelial function, characterized by reduced bioavailability of NO, has prognostic value for future cardiovascular events [19] and has been demonstrated for all established and also for newer cardiovascular risk factors like inflammation.

Acute and chronic systemic inflammation attenuates endothelial function. Experimental inflammation after infusion of salmonella thyphi vaccine induces endothelial dysfunction within 8 h in healthy volunteers [20]. Evidence for a potential role of chronic inflammation in atherogenesis comes from studies in patients with rheumatoid arthritis (RA). These patients show an increase in both cardiovascular morbidity and mortality [21]. Furthermore, striking similarities exist between the paradigm of inflammation in the pathogenesis of both atherosclerotic vascular disease and RA [22,23]. The shared features include involvement of cytokines, such as TNF-α and IL-6, raised concentrations of CRP, fibrinogen and amyloid-A, increased local expression of adhesion molecules and endothelin-1 [24]. These similarities suggest that inflammatory mechanisms also involve the vessel wall and facilitate the development of atherosclerotic lesions. Indeed, we recently demonstrated early endothelial dysfunction in patients with RA [25] providing an explanation for the excess cardiovascular morbidity in RA patients in whom traditional cardiovascular risk factors are usually absent [26].

Hypertension and vascular inflammation

Chronic inflammation presents with activation of the cyclooxygenase (COX) system, increased production of ROS and increased synthesis of CRP and pro-inflammatory cytokines, such as TNF-α and IL-6. An increasing body of evidence suggests that low-grade inflammation and oxidative stress account in part for hypertension-induced endothelial dysfunction and that CRP levels are associated with future development of hypertension [27–29]. Similar results have been provided by Engstrom *et al*. [30], showing that increased levels of inflammation-sensitive plasma proteins (fibrinogen, alpha1-antitrypsin, haptoglobin, ceruloplasmin and orosomucoid) are associated with an increased incidence of hypertension. Incident hypertension, the initiation of antihypertensive treatment, and self-reported systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg are increased in women with baseline CRP levels above 3.5 mg/l even after adjustment for cardiovascular risk factors [29]. Cross-sectional analysis of more than 15 000 women demonstrated a linear relationship between increasing blood pressure and increasing CRP levels [27]. During follow-up over 8 years both parameters were strong predictors for cardiovascular events, and the predictive values of CRP and elevated blood pressure in combination are additive. Interestingly, although low-dose aspirin has no effect on CRP levels, it has been shown to be effective in primary prevention in men. This effect, however, is greatest in persons with the highest levels of hs-CRP and declines in direct relation to CRP levels [31].

In untreated human hypertension, CRP levels have recently been found to be increasingly dependent on systolic blood pressure levels [32–35]. Most importantly, CRP increase is independently associated with other classical cardiovascular risk factors [32] and might be an independent risk factor for the development of hypertension after correction for age, sex, body mass index, family history of hypertension, fasting glycemia, sedentary behaviour, and alcohol consumption [34]. In addition, CRP is a strong risk factor for ischaemic stroke, independent of the severity of the underlying atherosclerotic disease [36,37]. A recent study investigated the relationship between IL-6, TNF-α, and hs-CRP with arterial stiffness in untreated hypertensive patients [38]. The authors demonstrated that hs-CRP, IL-6 and TNF-α are significantly related to pulse wave velocity, a marker of aortic stiffness, and augmentation index, a manifestation of wave reflection, in essential hypertension. These data suggest a pivotal role for inflammation in the development of vascular disease, hypertension in particular. However, initiation of inflammatory processes expands from hypertension towards the more complex metabolic syndrome, including pathologic glucose and lipid levels, visceral obesity and hypertension. Each component of the metabolic syndrome can induce vascular inflammation,

thus increasing cardiovascular risk. Therefore, a rationale for assessment of inflammation status and anti-inflammatory treatment in addition to anti-hypertensive treatment in atherosclerosis and hypertension is given and may increase clinical benefit.

Anti-inflammatory drugs and hypertension

Selective and non-selective COX-inhibitors

The impact of specific anti-inflammatory drugs, selective and non-selective COX-inhibitors (coxibs and NSAIDs), on cardiovascular homeostasis and the incidence of cardiovascular events have been discussed intensively over the last months.

Indeed, increased cardiovascular events have been observed with rofecoxib in the Vioxx Gastrointestinal Outcomes Research trial (VIGOR [39]) and Adenomatous Polyp Prevention on Vioxx (APPROVe [40]) trial as well as with celecoxib in the Adenoma Prevention with Celecoxib (APC) trial [41], pointing towards a potential class effect for coxibs. This 'class effect' for an increase in the risk of cardiovascular disease is thought to be related to preferential inhibition of prostacyclin over thromboxane and thus a tendency towards pro-thrombosis. However, data suggest differential effects of coxibs respect to cardiovascular risk. Thus, other mechanisms come into play and might counterbalance this pro-thrombotic effect. These include a differential impact on oxidative stress, inflammation markers, endothelial function, renal function and morphology and tissue factor expression and activity with potential beneficial effects for celecoxib but not for rofecoxib [42–46].

In addition to putative pro-thrombotic effects of these drugs, the impact on blood pressure levels and blood pressure control are important. Several studies revealed differences between commonly used drugs and within the group of selective COX-2 inhibitors, the coxibs. Rofecoxib is clearly associated with an increase in blood pressure and new onset of hypertension while celecoxib is comparable to other NSAIDs [47,48]. In patients with osteoarthritis, treatment with rofecoxib but not celecoxib or naproxen induced a significant increase in 24 h systolic BP. However, a destabilization of hypertension control occurred to some extent with all three drugs, while this phenomenon was seen more often in patients treated with rofecoxib than with the other therapies [49]. Similar data come from a recent meta-analysis of 19 randomized controlled trials involving coxibs and non-selective NSAIDs [50]. Selective COX-2 inhibitors were associated with blood pressure elevation compared with placebo and nonselective NSAIDs; however, there was a higher incidence of developing hypertension observed with rofecoxib compared with celecoxib.

Involved mechanisms might include a disturbance of sodium and water retention similar to that observed with classical non-selective NSAIDs. Early studies in healthy subjects showed that high doses of celecoxib, rofecoxib and NSAIDs induce a slight decrease in water, sodium and potassium excretion, but had no impact on blood pressure levels [51,52]. In users of NSAIDs, development of peripheral oedema and increases in blood pressure are associated with the development of chronic heart failure [53]. Further data on differences between coxibs come from a large observational study on the incidence of chronic heart failure during COX-inhibition. In over 38 000 patients who were started on rofecoxib, celecoxib or non-selective NSAIDs, rofecoxib and NSAIDs showed an adjusted rate-ratio of 1.8 and 1.4 respectively, while no increased risk of admission for congestive heart failure was observed for celecoxib [54].

Interestingly, ACE-inhibitors, beta blockers and diuretics, and to a lesser extent angiotensin II receptor blockers and calcium channel blockers, rely on the synthesis of vasodilator prostaglandins to exert their effects [55,56]. This is of particular interest, since prostacyclin levels can be reduced not only with selective COX-2 inhibitors but also with higher doses of classical NSAIDs [57]. This might translate into clinical practice, as recent data suggest that rofecoxib appears to interfere with the anti-hypertensive effects of ACE-inhibitors and beta-blockers, but not of calcium channel blockers [47].

While anti-hypertensive treatment is known to improve endothelial function as a surrogate for atherosclerosis, clinical and experimental studies also demonstrate that anti-inflammatory treatment has beneficial effects on vascular function. In patients with severe CAD, treatment with celecoxib reduces plasma levels of hs-CRP and oxidized-LDL, as markers of low-grade chronic inflammation and oxidative stress. This effect was accompanied by improved endothelial function [42]. Similar results were obtained in patients with arterial hypertension who were treated with celecoxib. Endothelial function improved within 3 h and remained so during the treatment course [43]. A comparative study of celecoxib, rofecoxib and diclofenac on vascular function in salt-sensitive hypertensive rats showed that celecoxib, but not rofecoxib or diclofenac, improves endothelial function [44]. In addition, oxidative stress and inflammation markers were reduced by celecoxib alone. In a similar model, celecoxib improved proteinuria, renal and pre-glomerular vessel morphology and reduced the number of macrophages and CRP-mRNA in renal cortex of the hypertensive animals [45].

ACE-inhibitors and angiotensin receptor blockers

Several large randomized trials demonstrated a reduction in the incidence of recurrent cardiovascular events and mortality with ACE-inhibitor therapy [58–60]. In addition, ACE-inhibitors and angiotensin receptor blockers exert anti-inflammatory effects particularly by inhibiting pro-inflammatory effects of angiotensin II [61]. Olmesartan treatment significantly reduced serum levels of hs-CRP, TNF-α, IL-6, and monocyte chemotactic protein-1 after 6 weeks of therapy in patients with

essential hypertension, suggesting that this anti-inflammatory action of angiotensin II receptor antagonists may contribute to their beneficial cardiovascular effects. The stimulation of cytokines by angiotensin II seems to be mediated via an activation of nuclear factor-κB (NF-κB) dependent pathway, which can be blocked, by losartan and candesartan [62,63].

Statins

Statin treatment significantly reduces the number of cardiovascular events, particularly in secondary prevention [64,65]. For better guidance of cholesterol levels to reduce cardiovascular risk with statins, monitoring of CRP might be helpful, because statins lower LDL cholesterol and CRP. The relationships between LDL cholesterol and CRP levels after treatment with atorvastatin or pravastatin and the risk of recurrent myocardial infarction or death from coronary causes were evaluated among 3745 patients with acute coronary syndromes [66]. Both statins lowered cholesterol levels, although atorvastatin was more likely than pravastatin to result in low levels of LDL cholesterol and CRP. Patients who had LDL cholesterol levels of less than 70 mg/dl and CRP levels of less than 1 mg/l after statin therapy had the lowest rate of recurrent events, demonstrating that patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. To further investigate the impact of statin treatment in the primary prevention of cardiovascular disease in patients with low LDL-cholesterol but elevated hs-CRP levels, the JUPITER trial has recently been initiated [67].

PPAR gamma activators

Other widely described drugs for patients with cardiovascular risk factors like hypertension, metabolic syndrome and type 2 diabetes, peroxysome proliferator-activated receptor (PPAR)-alpha and -gamma activators, seem to have anti-inflammatory properties. Indeed, PPAR-alpha activators like fenofibrate inhibit myocardial inflammation in angiotensin II-infused and salt-induced hypertensive rats [68,69]. In a similar model, angiotensin II-induced hypertensive rats received the PPAR-gamma activators pioglitazone or rosiglitazone. Both drugs reduced upregulated cell cycle proteins and pro-inflammatory mediators like NF-κB, VCAM and PECAM and improved endothelial function, and attenuated blood pressure increase and expression of angiotensin II type 1 receptors [70]. The anti-inflammatory effects of pioglitazone seem to be independent of glucose control, as demonstrated recently in a prospective study in 192 patients with type 2 diabetes [71]. Therefore, in view of the evolving epidemic of the metabolic syndrome with arterial hypertension and hyperglycaemia, additional effects of drugs for the control of single components of the metabolic syndrome are important.

Cannabinoid receptor antagonist

This might hold also for a very new class of drugs interacting with the endocannabinoid system, the cannabinoid-1 receptor in particular. Originally developed to help smoking cessation, rimonabant has favourable effects on body weight, waist circumference, insulin resistance and dyslipidaemia [72]. In normotensive animals no effect on blood pressure levels is observed but in hypertensive animals, rimonabant lowers blood pressure and reduces cardiac contractility [73]. In addition, rimonabant has potent anti-inflammatory activity, as demonstrated in several animal models [74,75]. However, data from large-scale human studies show that effects on blood pressure are only mild and data on impact on inflammation markers are as yet unavailable.

Conclusion

Inflammation plays a pivotal role in the development and progression of atherosclerosis. Like other risk factors, arterial hypertension is associated with a pro-inflammatory status. However, the 'inflammation in atherosclerosis hypothesis' remains still to be challenged in prospective clinical trials. Indeed, unless anti-inflammatory treatment strategies provide benefit for patients, inflammation may thus face the fate of some other cardiovascular risk factors that, notwithstanding their potential pathophysiological relevance, are considered as lost in translation into clinical practice.

Conflict of interest statement. Dr Ruschitzka has served as a consultant or received speaker fees from Aventis, Bayer, Merck, Noratis and Pfizer.

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